

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 302 582 B2

(12)

NEW EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the opposition decision:
17.12.1997 Bulletin 1997/51

(51) Int. Cl.⁶: **A61K 9/54, A61K 38/04**

(45) Mention of the grant of the patent:
27.07.1994 Bulletin 1994/30

(21) Application number: 88302940.7

(22) Date of filing: 31.03.1988

(54) Drug delivery system and method of making the same

System zur Freisetzung von Medikamenten und dessen Herstellungsmethode

Système pour la libération de drogues et son mode de préparation

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(30) Priority: 03.08.1987 US 81289

(43) Date of publication of application:
08.02.1989 Bulletin 1989/06

(73) Proprietor:
SOUTHERN RESEARCH INSTITUTE
Birmingham Alabama 35255-5305 (US)

(72) Inventors:
• Tice, Thomas R.
Birmingham Alabama 35244 (US)
• Gilley, Richard M.
Birmingham Alabama 35243 (US)

(74) Representative:
Dean, John Paul et al
Withers & Rogers
4 Dyer's Buildings
Holborn
London EC1N 2JT (GB)

(56) References cited:

EP-A- 0 052 510 EP-A- 0 058 481
EP-A- 0 202 065 EP-B- 0 218 928
WO-A-87/06129

- JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 73, no. 9, September 1984, pages 1294-1297, American Pharmaceutical Association; L.M. SANDERS et al.: "Controlled release of a luteinizing hormone-releasing hormone analogue from Poly(D,L-lactide-co-glycolide) microspheres"
- Holland et al., J. Controlled Release, Vol.4, pp.155-180 (1986)
- Wise et al., "Lactic/Glycolic Acid Polymers," Drug Carriers Biology and Medicine, Hrsg. Gregoriadis Academic Press, pp.237-270 (1979)
- Wise et al., Advanced Drug Delivery Reviews 1, pp.19-39 (May 1987)
- Bauer et al., Pharmazeutische Technologie, Georg Thieme Verlag Stuttgart, New York, pp.550-553 (1986)
- Beck et al., Res. Front.Fertil. Regul. (Proc.Int. Workshop), Ed.Zatuchni-Labbok-Sciarra, pp.213-229 (1980)
- Beck et al., Long-Acting Steroid Contraception, Ed. Daniel R.Mishell, Jr., Raven Press, New York pp.175-199 (1983)
- Sanders et al., Arch.Androl., Vol. 9, No.1, pp.91-92 (1982)
- Sanders et al., J. Pharm. Sciences, Vol.75, No.4, pp.356-360 (April 1986)
- Hutchinson et al., Biochem. Soc. Transactions, Vol.13, pp. 520-523 (1985)

EP 0 302 582 B2

Description

This invention relates to a composition capable of delivering an effective amount of a constant dose of bioactive molecule at a constant rate and in particular to a drug delivery composition.

It is known that a marked inhibition of pituitary and gonadal function that occurs after chronic administration of the [D-Trp⁶,des-Gly¹⁰]-LHRH ethylamide an analog of luteinizing hormone releasing hormone (LHRH) and other LHRH analogs leads to a reduction in steroidal sex hormones and makes possible approaches for the use as a contraceptive or for the treatment of sex hormone-dependent tumours. Concerning the latter, studies involving rats treated with LHRH analogs show the potential clinical efficacy of the hormone in the treatment of prostrate carcinoma and other hormone-dependent tumours in animals.

The treatment of hormone-dependent tumours and other disorders in animals would be greatly enhanced by a delivery system which, after a single administration, maintained controlled levels of active ingredients, including [D-Trp⁶,des-Gly¹⁰]-LHRH ethylamide and its related analogs, over extended periods of time. Traditional methods of administering peptides (or proteins) result in high initial concentrations of peptide (or protein) analog in the tissue, but over a short period of time, i.e., over a few minutes to several hours, peptide levels in the blood decline. Therefore, optimal pharmacological effects are most often not achieved. The result is a need for more frequent administration of higher-dosage regimens.

More recently, a polymer of poly(D,L-lactide-co-glycolide) (DL-PLG), which is biodegradable and biocompatible with living tissue, has been used in microcapsules for longer acting delivery systems. Systems of microencapsulated active ingredients in polymers and copolymers of lactic acid and glycolic acid have been used to achieve controlled release of chemical and biological pharmaceuticals. For example, U.S. Patent No. 3,773,919 discloses a drug, stated to include water-soluble antibiotic peptides encapsulated in lactide/glycolide copolymers so as to provide controlled release. Canadian Patent No. 1,176,565 discloses a microcapsule composition comprising a core containing a LHRH peptide encapsulated in a biodegradable, biocompatible copolymer excipient.

Microencapsulation for controlled release of enzymes, hormones and other biologicals are discussed in papers by Sanders, Kent, McRae, Vickery, Tice, and Lewis, *Journal of Pharmaceutical Sciences*, Vol. 73, pp. 1294-1296, September 1984 and by Redding, Schally, Tice and Meyers, *Proc. Natl. Acad. Sci. USA*, Vol. 81, pp. 5845-5848, September 1984. The first paper describes a system controlled by diffusion and erosion, wherein the kinetics of compound release determined by the parameters of the copolymer, and more particularly, the controlled release of nafarelin acetate, an analog of LHRH, from poly(D,L-lactide-co-glycolide) microspheres. The second paper discloses the inhibition of rat prostrate tumours by controlled release of [D-Trp⁶] luteinizing hormone-releasing hormone from injectable microcapsules.

The microcapsule systems described in the above-publications all share a common feature in that the release of the compound is controlled by the porosity and/or erosion of a polymer continuum. Also, all the described microcapsule systems utilize only a single type of copolymer. Therefore, while a controlled release of the compound is achieved, such is limited by the specific lactide/glycolide ratio used in the encapsulating material. At the most, the methods previously used, and particularly the peptide microcapsule, provided release times of approximately one month.

WO 87/06129 discloses a sustained release implant comprising a plurality of biodegradable microcapsules containing a physiologically active ingredient, the microcapsules being embedded in a biodegradable polymeric article. This document does not disclose how to produce sustained release of the bioactive ingredient at a constant rate.

There exists, therefore, a need for a method of delivering active ingredients, including peptides, proteins and other bioactive molecules used in treating disease, which utilize the advantages of microencapsulation, but which provides a longer controlled duration of release than that presently known. Also, there exists a need for a method of providing a constant dose regime of active ingredient throughout the longer release time provided by using biodegradable microcapsules.

According to the present invention there is provided a parenteral administration composition capable of delivering an effective amount of a constant dose of bio-active molecule at a constant rate to an animal over a preselected, prolonged period of time, comprising a blend of free-flowing microcapsules in which effective amounts of a bioactive molecule are encapsulated in at least two biodegradable and biocompatible copolymer excipients to form first and second microcapsules, each excipient capable of a different rate of release of said molecule therethrough, said composition having a delivery profile wherein the release of said molecule through said second microcapsule begins as the release of said ingredient through said first microcapsule declines. This allows the delivery of an active ingredient into the system of an animal at a constant rate over a long period of time, i.e one and one-half to six months or longer. Preferably, the composition comprises a blend of free flowing spherical particles and an effective amount of the microcapsule blend may be administered to the animal parenterally (e.g intravenously, intramuscularly, subcutaneously, intranasally, intraperitoneally, or by inhalation).

A quantity of these particles are of such a copolymer excipient that the core active ingredient is released quickly after injection, and thereby delivers the ingredient for an initial period. A second quantity of the particles are of such type excipient that delivery of the encapsulated ingredient begins as the first quantity's delivery begins to decline. A third

quantity of ingredient may be encapsulated with a still different excipient which results in delivery beginning as the delivery of the second quantity begins to decline. Obviously, still greater assortments of excipients can be used to obtain more prolonged release time of the encapsulated ingredient. A further modification of the present invention could be to have different ingredients encapsulated within a blend of varying excipient formulations.

It is shown, therefore, that as the usefulness of one type of particle begins to decline or run out, another type begins to take over. This provides a preselected, constant rate of delivery over a prolonged period of time. For example, by varying the lactide/glycolide ratio in a poly(D,L-lactide-co-glycolide) encapsulation, as well as the types and quantities of encapsulated active ingredient, it is possible to design a long-term, controlled-release profile of choice.

More particularly, the invention relates to a compatible, biodegradable, injectable microcapsule delivery system for the peptide agonist [D-Trp⁶,des-Gly¹⁰]-LHRH ethylamide (hereinafter referred to as the "agonist") and for the peptide antagonist [D-N-Ac-4-Cl-Phe²,D-Trp⁶,D-Ala¹⁰]-LHRH (or an LHRH antagonist of similar structure) (hereinafter referred to as the "antagonist"). The microcapsule formation consists of free-flowing spherical particles, preferably of poly(D,L-lactide-co-glycolide) which can be administered parenterally, (e.g. intravenously, intramuscularly, subcutaneously, intranasally, intraperitoneally or by inhalation). By utilizing a combination of various polymers with different lactide/glycolide ratios, one can greatly prolong the release profile of the encapsulated LHRH analog. Delivery periods of six months or more can be achieved.

In one aspect of the invention the biocompatible microcapsule delivery system is for the agonist [D-Trp⁶,des-Gly¹⁰]-LHRH ethylamide which delivers the agonist at a constant rate of 50 µg to 250 µg or more per day for a duration of from one and one-half to six months or more in men and women.

In another aspect of the invention the biocompatible, biodegradable microcapsule delivery system is for the antagonist [D-N-Ac-4-Cl-Phe²,D-Trp⁶,D-Ala¹⁰]-LHRH, or an LHRH antagonist of similar structure, which delivers that antagonist at a constant rate of 200 µg to 500 µg or more per day for a duration of from one to three months or more.

An illustration of the method of preforming one embodiment of the invention, that is, the use of LHRH agonist encapsulated in poly (D,L-lactide-co-glycolide), follows. In addition, the details and results of a study utilizing this embodiment in rats are provided.

It should be noted, that other polymers besides poly(D,L-lactide-co-glycolide) may be used. Examples of such polymers include, but are not limited to: polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybutyrate and copolymers thereof, polymaleamides, copolyoxalates and polysaccharides.

I. PREPARATION OF DL-PLG EXCIPIENTS

The general procedures used to prepare DL-PLG copolymers and the results of their characterization are detailed in the following sections.

a. DL-Lactide Purification

DL-lactide was used to prepare the polymers. To purify the monomer, it is first dissolved by heating a mixture of the monomer in a volume of dry (stored over molecular sieves) ethyl acetate about equal to its weight. While still hot, the solution is vacuum filtered through an extra coarse, fitted-glass gas-dispersion tube. The solvent level is reduced with an aspirator to a level equal to about half the weight of the lactide. The solution is then allowed to cool slowly to room temperature and chilled in an ice-water bath to effect crystallization. The monomer is finally filtered in a nitrogen-filled glove box. The monomer is recrystallized from ethyl acetate two additional times in this manner. All glassware used after the initial hot filtration and recrystallization is oven dried overnight at 150°C prior to use. After the final recrystallization, the purified monomer is vacuum dried in a desiccator and stored in oven-dried glass jars until ready for use.

b. Glycolide Synthesis and Purification

The glycolide monomer is prepared and purified by the following method: Excess water is first distilled from 67% aqueous glycolic acid (Eastman Chemicals, Rochester, N.Y.) in a 3-neck flask equipped with a thermometer, distillation head, and a condenser. The solution is boiled at reduced pressure with the use of a water aspirator. After the excess water has evolved, heating is continued to remove additional water by dehydration of the glycolic acid. After no further water is evolved, the flask is allowed to cool to room temperature under vacuum. At this point, about 1 percent by weight of antimony oxide, based on the theoretical glycolic acid content, is added to the flask as a catalyst. The distillation head and condenser are removed, and the flask is connected to two receiving flasks and a trap arranged in series. The receiving flasks and trap are cooled by dry-ice: isopropanol baths. (Note: The first receiving flask is for product collection. The second receiving flask is actually a trap). The pressure is reduced to about 266 N/m² (mmHg), and the reaction flask is heated to distill the crude glycolide. The material that distills between 110 and 130°C is collected in the first receiving flask.

The crude glycolide collected is next purified by first washing the product. This is achieved by slurring the glycolide in isopropanol, followed by filtering and vacuum drying, and then by three recrystallizations from ethyl acetate. After washing, precautions are made to protect the glycolide from atmospheric moisture during each stage of recrystallization by using oven-dried glassware, dry ethyl acetate (stored over molecular sieves), and a glove box filled with nitrogen.

5 The crude glycolide is combined with a volume of ethyl acetate approximately equal to three-fourths its weight. The mixture is then heated to reflux to dissolve the glycolide and cooled slowly to room temperature to allow crystallization. The monomer is recrystallized three times in this manner. After each recrystallization, the glycolide crystals are collected by vacuum filtration in a glove box. After the final recrystallization, the product is dried at room temperature under a vacuum of $<266 \text{ N/m}^2$ ($<2 \text{ mmHg}$) in a desiccator. The purified dried monomer is then stored in oven-dried glass jars placed
10 inside a desiccator.

c. Copolymer Synthesis

All glassware is oven dried at 150°C overnight and allowed to cool in a nitrogen-filled glove box. All handling of the reactants and assembling of apparatus is done in the glove box. The purified monomers are weighed directly into a 3-neck, round-bottom flask. After being charged and sealed, the flask assembly is evacuated three times, back filled with nitrogen, removed from the glove box, connected to a dry nitrogen purge, and placed into an oil bath maintained at 170°C . Once the monomers have partially melted, stirring is begun. Positive nitrogen pressure is maintained over the monomers throughout the polymerization. After the monomers have completely melted, 0.05 percent by weight of stannous octoate is introduced into the flask with a microsyringe. Stirring is continued until the mixture becomes too viscous to stir, at which point the stirrer is raised out of the melt. The polymerization is then continued for a total reaction time to 16 to h. Next, the resulting polymer is allowed to cool to room temperature under nitrogen atmosphere and removed by breaking the flask. Any residual glass is removed from the polymer plug by submerging it into liquid nitrogen. While cold, the polymer is broken into several smaller pieces and dissolved in methylene chloride and precipitated into methanol. The solvent is then removed by evaporation at room temperature under a hood and, finally, under vacuum at $<266 \text{ N/m}^2$ ($<2 \text{ mmHg}$) and about 40°C . The yields are typically about 75% of theoretical. The polymers are then characterized and stored in a desiccator until ready for use.

II. PREPARATION AND CHARACTERIZATION OF AGONIST LHRH MICROCAPSULES

30 The phase-separation microencapsulation process is used in this example to prepare microcapsules with the LHRH agonist and DL-PLG excipients. DL-PLG is dissolved in methylene chloride and placed in a resin kettle equipped with a true-bore stirrer that is fitted with a 3.75cm. Teflon[®] turbine impeller and powered by a Fisher Stedi-speed stirrer at a speed of about 3000 rpm. The peptide is then dispersed in the stirrer copolymer solution followed by the addition of silicone oil (Dow 200 Fluid, $3.5 \times 10^{-4} \text{ m}^2/\text{s}$ (350 cSt), Dow Corning Corp., Midland, MI) to the resin kettle. This silicone oil causes the DL-PLG to coacervate and deposit onto the peptide particles. Immediately after the silicone addition is complete, the contents of the resin kettle are poured into 2 l of heptane being stirred at about 800 rpm with a 5 cm (2 in.) stainless steel impeller. The heptane causes the microcapsules to harden by extracting methylene chloride out of the microcapsules. After the stirring is continued for 30 min., the hard microcapsules are isolated by filtration and dried for 24 hours in a vacuum desiccator maintained at room temperature.

40 The core loading of the microcapsules is a measure of the amount of LHRH incorporated inside the microcapsules. This analysis is based on the extraction of core material (LHRH) from a known amount of microcapsules and quantification of the extracted LHRH by high performance liquid chromatography. A known amount of microcapsules is dissolved in methylene chloride. The LHRH is then extracted into triethylammonium phosphate (TEAP) buffer (pH 2.5) and is injected into an HPLC for quantification.

45 The theoretical core loading for a batch of microcapsules is based upon the copolymer and LHRH input and is calculated in the following manner:

$$\text{Theoretical Core Loading, wt \%} = \frac{\text{peptide input, g}}{(\text{copolymer input, g}) + (\text{peptide input, g})} \times 100$$

The actual core loading is determined by assaying the microcapsules by the procedure described above. The actual core loading is calculated in the following manner:

$$\text{Actual Core Loading, wt \%} = \frac{\text{peptide assayed, g}}{\text{amt of microcapsules used in assay, g}} \times 100$$

The encapsulating efficiency is the ratio of the actual and theoretical core loadings and is calculated in the following manner:

$$\text{Encapsulation Efficiency, \% of theoretical} = \frac{\text{Actual Core loading, wt \%}}{\text{Theoretical core loading, wt \%}} \times 100$$

III. PHARMACOKINETICS STUDIES OF AGONIST MICROCAPSULES IN RATS

Pharmacokinetics studies were performed involving the microencapsulation of agonist LHRH in DL-PLGs with varying lactide/glycolide ratios. A formulation of a blend of agonist microcapsules prepared with mole ratios of 52:48, 68:32, and 85:15 DL-PLG excipients were used. This blend consisted of appropriate amounts of 3%-loaded agonist microcapsules prepared with 52:48 DL-PLG, 10%-loaded agonist microcapsules prepared with 68:32 DL-PLG, and 8% loaded agonist microcapsules prepared with 85:15 DL-PLG excipients. The 52:48 DL-PLG component of the blend was designed to deliver agonist during the first month after administration of the microcapsules. The 68:32 DL-PLG component was designed to release the agonist primarily during the second month after administration, and the 85:15 component was designed to release the agonist primarily during the third through sixth months. Overall, the blend was designed to release approximately 50 µg of agonist per day for 180 days.

Studies with the agonist microcapsules were initiated. A total of 80 male rats were used in the studies. Three groups of 20 rats each were administered three agonist microcapsule formulations, and one group of 20 rats (a control group) was administered placebo microcapsules (empty microcapsules). Blood was collected for six months from the animals receiving the prototype six months formulation, the 85:15 formulation, and the placebo microcapsules. Blood was collected for four months from animals treated with the agonist microcapsule formulation prepared with 68:32 DL-PLG. Ten rats from each group were bled on Fridays. Agonist serum levels were determined for all 80 rats during month 1. Thereafter, agonist serum levels were determined only for rats bled on Fridays.

CONCLUSION

The levels of agonist serum were determined using radio-immunoassay (RIA). RIA results from serum samples collected during the test period showed that a constant release of agonist LHRH was released over the six months. Correspondingly, the concentration of testosterone in serum was found to be suppressed to castrate levels during the controlled release of the LHRH from the single injection of similar microcapsules. After approximately six months, when the microcapsules were depleted of their LHRH, the testosterone levels returned to normal.

Table 1 and Figure 1 show the agonist serum levels obtained with the prototype six-month agonist microcapsule formulation.

Table 2 shows the agonist serum levels obtained with agonist microcapsules prepared with 85:15 DL-PLG.

Table 3 shows the agonist serum levels obtained with agonist microcapsules prepared with 68:32 DL-PLG.

Table 4 shows the results of the control group study using placebo microcapsules.

TABLE 1. AGONIST SERUM LEVELS OBTAINED WITH PROTOTYPE SIX-MONTH AGONIST MICROCAPSULE FORMULATION: COMPOSITE D196-150S

Group	Serum collection date	Day	LHRH in serum, pg/mL ^a										Average LHRH in serum, pg/mL ± SE
			Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	
A	6-24-85	0	99	118	99	99	99	99	99	99	99	99	101 3.4
B	6-26-85	0	99	100	99	100	99	100	100	100	99	99	100 0.5
A	7-02-85	8	1515	2555	1604	972	1127	1240	617	995	746	2050	1342 470.9
B	7-02-85	11	2113	2141	2423	1613	5416	3174	3549	3673	3602	3791	3174 836.8
A	7-03-85	15	1541	1549	1695	1777	1751	1110	823	1624	893	2013	1478 281.5
B	7-12-85	18	548	819	945	706	516	989	655	761	790	687	748 125.2
A	7-16-85	22	2016	1007	1503	2334	1880	1033	1101	1492	1005	2150	1558 425.5
B	7-18-85	25	750	653	774	723	796	1112	638	703	804	988	794 104.9
A	7-23-85	29	1658	2181	1723	1257	2657	1481	1937	2269	1866	1432	1046 335.9
B	7-26-85	32	3322	3701	5424	3871	4596	4254	4008	4885	3643	4493	4260 551.8
A	7-30-85	36	3893	5228	3050	2805	3909	2084	2356	5228	3898	1546	3400 1031.1
B	8-02-85	39	1961	1727	1637	2415	1710	1899	1750	2683	1902	2340	2002 286.2
A	8-07-85	46	5444	2921	4212	4534	3838	5008	2059	3827	2455	3044	3814 795.6
B	8-16-85	53	3340	1456	2104	2264	1433	3077	2486	4589	1834	2444	2505 680.5
A	8-23-85	60	2083	2847	2104	2181	2639	3243	2777	4544	2135	1631	2623 587.0
B	8-30-85	67	3319	1975	2023	1883	2384	2741	3480	2124	3889	1851	2387 656.3
A	9-04-85	74	5017	2671	3628	4508	2318	4639	4207	3940	4563	3223	3859 759.5
B	9-13-85	81	5206	5084	5114	5857	3154	7253	6765	5303	7316	6163	5721 949.1
A	9-20-85	88	4356	6119	4297	5007	2793	3831	2482	2485	4796	2552	3482 1053.2
B	9-27-85	95	4997	1856	2425	2022	1220	5916	2742	3095	2271	1227	2777 1135.3
A	10-04-85	102	2055	1407	1907	1864	1234	3111	2083	2805	2284	1844	2079 433.1
B	10-11-85	109	4381	4034	3959	4257	2227	3592	3960	4381	4381	3697	3847 428.2
A	10-18-85	116	3182	1206	1697	1409	823	ND ^b	2349	1468	3283	2382	1998 700.3
B	10-24-85	123	1838	1962	3592	1592	1402	ND	2340	2344	3402	4040	2730 871.7
A	11-01-85	130	2851	1199	2026	1368	982	ND	1275	2204	3642	1819	1954 654.7
B	11-08-85	137	1230	1194	2320	1716	1222	ND	1602	2013	1712	1041	1518 346.7
A	11-15-85	144	1463	933	1966	1184	1416	ND	1440	1889	1503	1394	1465 206.4
B	11-22-85	151	910	872	2343	1370	1560	ND	1355	2497	1571	1058	1493 441.3
A	11-29-85	158	554	906	1447	1015	1626	ND	1040	2623	1465	842	1280 463.5
B	12-06-85	164	295	350	677	510	411	ND	427	834	636	384	503 145.7
A	12-13-85	171	259	378	492	519	391	ND	369	882	459	343	477 127.1
B	12-20-85	178	275	513	755	442	392	ND	637	532	511	269	461 106.1
A	12-27-85	185	227	349	599	640	590	ND	355	610	518	324	468 134.6
B	1-03-86	192	155	382	614	513	548	ND	666	783	515	360	486 128.2

^aSerum samples were analyzed at Research Triangle Institute using radioimmunoassay.

^bND = Not determined.

TABLE 2. AGONIST SERUM LEVELS OBTAINED WITH ACONIST MICROCAPSULES
PREPARED WITH 85:15 DL-PLG: COMPOSITE D196-060-1S

Group	Serum collection date	Day	LHM in serum, pg/mL ^a										Average LHM in serum, pg/mL ± SE		
			Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10			
C	6-24-85	0	100	100	99	100	100	100	99	100	99	99	100	100	0.5
D	6-24-85	0	100	99	913	100	130	100	100	99	124	115	99	188	145.0
C	7-02-85	8	491	1078	950	504	1097	1278	1259	1259	1077	1061	1632	1065	237.1
D	7-03-85	11	2806	2613	2921	1465	1933	2390	2332	2474	3357	1489	2480	2446.2	274.0
C	7-09-85	15	642	783	778	1961	973	966	610	1215	730	704	936	936	60.6
D	7-12-85	18	488	426	248	582	384	314	453	402	506	425	423	423	100.6
C	7-16-85	22	1417	460	609	1451	354	521	800	1118	543	539	781	781	232.2
D	7-19-85	25	441	346	315	491	770	191	480	508	471	477	449	449	100.6
C	7-23-85	29	932	469	432	581	274	357	414	345	282	256	430	430	136.6
D	7-26-85	32	384	467	964	1098	510	360	842	773	1202	573	717	717	258.5
C	7-30-85	36	1291	772	513	426	351	553	461	312	398	356	543	543	197.2
D	8-02-85	39	343	223	298	417	265	252	347	293	342	296	308	308	43.4
C	8-09-85	46	979	908	568	1119	825	262	1366	895	1506	1053	956	956	264.5
D	8-16-85	53	1679	1301	1817	1368	617	941	1332	1492	1697	1031	1408	1408	295.7
C	8-23-85	60	2197	1981	1173	525	1945	1590	1993	2313	3116	1650	1864	1864	507.0
D	8-30-85	67	2232	2449	2004	1319	1132	2196	1760	3635	2088	2039	2084	2084	435.6
C	9-06-85	74	5206	4433	2616	2882	1381	4311	3692	3676	2113	1953	3207	3207	1017.1
D	9-13-85	81	4187	3738	3742	3627	3559	4594	2702	3977	3383	3500	3791	3791	637.1
C	9-20-85	88	2365	3549	2272	2310	5396	5202	2834	1874	4697	2708	3321	3321	1112.2
D	9-27-85	95	3494	2938	1466	1812	1439	1411	1642	1162	2119	1414	1893	1893	560.6
C	10-04-85	102	2911	4381	3878	2230	2094	1938	3168	1677	3461	1841	2758	2758	801.9
D	10-11-85	109	3619	4381	4286	4381	4381	2745	4381	4381	4381	3232	4018	4018	689.5
C	10-18-85	116	1323	2365	1684	1235	1080	886	1296	1747	1309	1060	1371	1371	276.9
D	10-25-85	123	3781	2312	2323	1875	2400	1625	7735	2672	1408	3132	2966	2966	1169.8
C	11-01-85	130	1620	1937	1819	1720	1577	1078	4031	2498	1559	2205	2112	2112	695.4
D	11-08-85	137	1588	1244	1695	2511	1168	1199	3514	3094	1893	1340	1925	1925	669.0
C	11-15-85	144	1736	1450	1874	1060	1297	804	5439	2697	1756	2111	2004	2004	806.8
D	11-22-85	151	2638	1279	1760	1720	1319	1124	3521	2546	1418	1502	1885	1885	616.2
C	11-29-85	158	1645	1301	1777	1119	1048	670	4319	1800	1174	1396	1625	1625	630.8
D	12-06-85	164	748	680	780	533	724	396	970	580	784	535	672	672	100.3
C	12-13-85	171	715	ND ^b	816	740	699	349	1227	925	757	708	771	771	176.3
D	12-20-85	178	605	ND	555	395	488	241	807	604	514	504	531	531	105.4
C	12-27-85	185	572	ND	584	384	422	260	832	543	605	513	523	523	115.9
D	1-03-86	192	521	ND	666	514	660	314	1029	636	811	492	627	627	140.7

^aSerum samples were analyzed at Research Triangle Institute using radioimmunoassay.
^bND = Not determined.

TABLE 3. AGONIST SERUM LEVELS OBTAINED WITH AGONIST MICROCAPSULES
PREPARED WITH 68:32 DL-PLG: COMPOSITE D196-059-1S

Group	Serum collection date	Day	LNHH in serum, pg/mL ^a										Average LNHH in serum, pg/mL ± SE
			Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	
E	6-24-85	0	99	672	100	100	100	126	102	100	100	99	156
F	6-24-85	0	100	99	99	99	158	100	100	100	89	100	104
E	7-02-85	8	336	262	307	340	343	152	195	242	286	272	232
E	7-05-85	11	435	287	519	390	285	480	370	423	389	MD	398
E	7-09-85	15	578	262	182	287	356	522	276	183	565	333	354
F	7-12-85	18	380	206	201	230	274	268	MD ^b	197	248	MD	244
E	7-16-85	22	645	661	554	557	514	559	1100	307	976	521	641
F	7-19-85	25	147	217	257	172	175	218	MD	310	252	MD	219
E	7-23-85	29	1134	1200	483	719	865	992	855	544	2267	425	948
F	7-26-85	32	3798	910	1497	1542	1000	2060	MD	1313	835	MD	1619
E	7-30-85	36	1933	1079	1592	570	1815	1091	593	1582	1966	807	1303
F	8-02-85	39	2050	664	619	1040	396	457	MD	416	656	MD	792
F	8-09-85	46	1385	975	1221	1786	416	1478	MD	704	607	MD	1097
F	8-16-85	53	845	758	684	1031	501	859	MD	693	1073	MD	806
F	8-23-85	60	711	456	260	389	357	557	MD	374	731	MD	473
F	8-30-85	67	223	351	332	247	194	353	MD	264	524	MD	324
F	9-06-85	74	380	272	276	299	222	360	MD	287	312	MD	301
F	9-13-85	81	266	229	194	201	242	241	MD	188	223	MD	223
F	9-20-85	88	186	156	139	163	160	176	MD	163	253	MD	175
F	9-27-85	95	204	247	160	161	142	161	MD	136	176	MD	173
F	10-04-85	102	115	82	81	141	102	107	MD	77	100	MD	101
F	10-11-85	109	135	88	62	62	79	62	MD	62	64	MD	77

^aSerum samples were analyzed at Research Triangle Institute using radioimmunoassay.

^bMD = Not determined.

TABLE 4. CONTROL GROUPS FOR PHARMACOKINETICS STUDIES, PLACEBO MICROCAPSULES
PREPARED WITH 85:15 DL-PLG: COMPOSITE D196-105-1S

Group	Serum collection date	Day	LNH in serum, pg/mL ^a										Average LNH in serum, pg/mL ± SE
			Rat 1	Rat 2	Rat 3	Rat 4	Rat 5	Rat 6	Rat 7	Rat 8	Rat 9	Rat 10	
C	6-24-85	0	100	100	116	117	596	120	99	145	99	104	162 81.3
H	6-24-85	0	100	100	99	99	100	100	100	100	99	100	100 0.5
C	7-02-85	9	100	100	100	100	100	100	100	100	100	100	100 0.1
H	7-02-85	9	82	82	82	82	82	82	82	82	82	82	82 0.1
C	7-09-85	15	100	100	100	100	100	100	100	100	100	100	100 0.1
H	7-09-85	15	100	100	100	100	100	100	100	100	100	100	100 0.1
C	7-12-85	18	83	82	82	91	94	82	82	88	82	82	85 3.6
H	7-12-85	18	83	82	82	91	94	82	82	88	82	82	85 3.6
C	7-16-85	22	96	96	96	96	96	96	96	96	96	96	96 0.1
H	7-16-85	22	96	96	96	96	96	96	96	96	96	96	96 0.1
C	7-19-85	25	96	96	96	96	96	96	96	96	96	96	96 0.1
H	7-19-85	25	96	96	96	96	96	96	96	96	96	96	96 0.1
C	7-23-85	29	96	96	96	96	96	96	96	96	96	96	96 0.1
H	7-23-85	29	96	96	96	96	96	96	96	96	96	96	96 0.1
C	7-26-85	32	99	99	99	99	99	99	99	99	99	99	99 0.1
H	7-26-85	32	99	99	99	99	99	99	99	99	99	99	99 0.1
C	7-30-85	36	99	99	99	99	99	99	99	99	99	99	99 0.1
H	7-30-85	36	99	99	99	99	99	99	99	99	99	99	99 0.1
C	8-02-85	39	70	73	91	146	73	62	57	75	71	63	78 14.7
H	8-02-85	39	70	73	91	146	73	62	57	75	71	63	78 14.7
C	8-09-85	46	68	74	80	150	68	63	51	58	71	69	78 16.0
H	8-09-85	46	68	74	80	150	68	63	51	58	71	69	78 16.0
C	8-16-85	51	108	24	24	48	24	24	24	41	24	24	37 16.3
H	8-16-85	51	108	24	24	48	24	24	24	41	24	24	37 16.3
C	8-23-85	60	39	43	54	104	49	39	38	54	66	37	52 12.3
H	8-23-85	60	39	43	54	104	49	39	38	54	66	37	52 12.3
C	8-30-85	67	64	63	63	160	84	72	53	53	76	64	73 19.2
H	8-30-85	67	64	63	63	160	84	72	53	53	76	64	73 19.2
C	9-06-85	74	66	86	71	126	78	77	56	78	90	74	80 11.7
H	9-06-85	74	66	86	71	126	78	77	56	78	90	74	80 11.7
C	9-13-85	81	108	93	121	129	105	163	81	112	116	93	112 14.3
H	9-13-85	81	108	93	121	129	105	163	81	112	116	93	112 14.3
C	9-20-85	88	70	73	77	132	94	88	70	65	85	97	85 13.0
H	9-20-85	88	70	73	77	132	94	88	70	65	85	97	85 13.0
C	9-27-85	95	98	97	94	85	85	82	105	95	104	79	92 6.5
H	9-27-85	95	98	97	94	85	85	82	105	95	104	79	92 6.5
C	10-04-85	102	63	62	77	85	65	70	62	62	66	73	69 6.2
H	10-04-85	102	63	62	77	85	65	70	62	62	66	73	69 6.2
C	10-11-85	109	64	62	62	62	62	62	62	62	65	62	63 0.6
H	10-11-85	109	64	62	62	62	62	62	62	62	65	62	63 0.6
C	10-18-85	116	62	62	62	68	62	62	55	55	57	64	61 3.1
H	10-18-85	116	62	62	62	68	62	62	55	55	57	64	61 3.1
C	10-25-85	123	58	62	56	85	67	67	55	61	55	67	62 6.4
H	10-25-85	123	58	62	56	85	67	67	55	61	55	67	62 6.4
C	11-01-85	130	85	56	73	97	72	80	71	65	87	79	77 9.1
H	11-01-85	130	85	56	73	97	72	80	71	65	87	79	77 9.1
C	11-08-85	137	74	63	87	75	83	71	55	64	73	60	71 7.8
H	11-08-85	137	74	63	87	75	83	71	55	64	73	60	71 7.8
C	11-15-85	144	89	89	89	89	89	89	89	89	89	89	89 0.0
H	11-15-85	144	89	89	89	89	89	89	89	89	89	89	89 0.0
C	11-22-85	151	92	89	89	89	89	89	89	89	96	89	90 1.6
H	11-22-85	151	92	89	89	89	89	89	89	89	96	89	90 1.6
C	11-29-85	158	89	89	89	89	89	89	89	89	89	89	89 0.0
H	11-29-85	158	89	89	89	89	89	89	89	89	89	89	89 0.0
C	12-06-85	164	89	89	89	93	89	89	89	89	89	89	89 0.7
H	12-06-85	164	89	89	89	93	89	89	89	89	89	89	89 0.7
C	12-13-85	171	102	102	102	102	102	102	102	102	103	102	102 0.2
H	12-13-85	171	102	102	102	102	102	102	102	102	103	102	102 0.2
C	12-20-85	178	102	103	102	102	102	102	102	102	102	102	102 0.2
H	12-20-85	178	102	103	102	102	102	102	102	102	102	102	102 0.2
C	12-27-85	185	102	102	102	102	102	102	102	102	102	102	102 0.2
H	12-27-85	185	102	102	102	102	102	102	102	102	102	102	102 0.2
C	1-03-86	192	111	108	102	102	107	105	102	102	102	102	105 3.0
H	1-03-86	192	111	108	102	102	107	105	102	102	102	102	105 3.0

^aSerum samples were analyzed at Research Triangle Institute using radioimmunoassay.

Claims

1. A parenteral administration composition capable of delivering an effective amount of a constant dose of bio-active molecule at a constant rate to an animal over a preselected, prolonged period of time, comprising a blend of free-

flowing microcapsules in which effective amounts of a bioactive molecule are encapsulated in at least two biodegradable and biocompatible copolymer excipients to form first and second microcapsules, each excipient capable of a different rate of release of said molecule therethrough, said composition having a delivery profile wherein the release of said molecule through said second microcapsule begins as the release of said bioactive molecule through said first microcapsule declines.

2. A composition as claimed in claim 1, wherein said copolymer excipients are poly(D,L-lactide-co-glycolide).
3. A composition as claimed in claim 2, wherein said copolymer excipients have mole ratios of lactide to glycolide of 40:60 to 100:0, respectively.
4. A composition as claimed in claim 1, wherein said bioactive molecule is a peptide.
5. A composition as claimed in claim 4, wherein said peptide is hormonally active.
6. A composition as claimed in claim 4, wherein said peptide is a luteinizing hormone releasing hormone or an analog thereof.
7. A composition as claimed in claim 6, wherein said luteinizing hormone releasing hormone is [D-Trp⁶, des-Gly¹⁰]-LHRH ethylamide.
8. A composition as claimed in claim 1, wherein said bioactive molecule is a protein.
9. A composition as claimed in claim 1, wherein said blend of microencapsulated peptide is comprised of appropriate amounts of 3% by weight loaded [D-Trp⁶, des-Gly¹⁰]-LHRH ethylamide encapsulated in a copolymer excipient having a mole ratio of 52% lactide to 48% glycolide, and 10% weight loaded [D-Trp⁶, des-Gly¹⁰]-LHRH ethylamide encapsulated in a copolymer excipient having a mole ratio of 68% lactide to 32% glycolide.
10. A composition as claimed in claim 9 and further comprising an appropriate amount of 8% by weight loaded [D-Trp⁶, des-Gly¹⁰]-LHRH ethylamide encapsulated in a copolymer excipient having a mole ratio of 85% lactide to 15% glycolide added to said blend.
11. A composition as claimed in claim 10, wherein said blend delivers [D-Trp⁶, des-Gly¹⁰]-LHRH ethylamide at a constant rate of 50 µg to 250 µg per day for 180 days.
12. A composition as claimed in claim 4, wherein said peptide is [D-N-Ac-4-Cl-Phe², D-Trp⁶, D-Ala¹⁰]-LHRH or an LHRH antagonist analog.
13. A composition as claimed in claim 12, wherein said blend delivers [D-N-Ac-4-Cl-Phe², D-Trp⁶, D-Ala¹⁰]-LHRH or LHRH antagonist analog at a constant rate of about 200 µg per day for at least 90 days.
14. A method of preparing a parenteral administration composition according to claim 1 for delivering an effective amount of constant dose of a bioactive molecule to an animal over a preselected, prolonged period of time, comprising the steps of:
 - (a) encapsulating effective amounts of said bioactive molecule in first and second separate biodegradable and biocompatible copolymer excipients to form first and second microcapsules, each of said microcapsules capable of a different rate of release therefrom of said molecule; and
 - (b) combining an effective amount of said first and second microcapsules to form said composition having a delivery profile wherein the diffusion of said molecule through said second microcapsule begins as the release of said bioactive molecule through said first microcapsule declines.
15. The method as claimed in claim 14, wherein said first and second copolymer excipients have different monomer ratios.
16. A method as claimed in claim 14, wherein said excipient is selected from the group consisting of polyacetal polymers, polyorthoesters, polyesteramides, polycaprolactone and copolymers thereof, polycarbonates, polyhydroxybutyrate and copolymers thereof, polymaleamides, copolyoxalates, and polysaccharides.

Patentansprüche

1. Zusammensetzung für die parenterale Verabreichung, die zur Freisetzung einer wirksamen Menge einer konstanten Dosis eines bioaktiven Moleküls bei einer konstanten Geschwindigkeit an ein Tier über eine vorgängig ausgewählte längere Zeitdauer befähigt ist, wobei die Zusammensetzung ein Gemisch freifließender Mikrokapseln umfaßt, in denen wirksame Mengen eines bioaktiven Moleküls in wenigstens zwei biologisch abbaubaren und biologisch verträglichen Copolymerarzneimittelträgern zur Bildung von ersten und zweiten Mikrokapseln verkapselt sind, wobei jeder Arzneimittelträger zu einer anderen Geschwindigkeit für die Freisetzung des Moleküls aus den Mikrokapseln befähigt ist und die Zusammensetzung ein Freisetzungsprofil aufweist, bei dem die Freisetzung des Moleküls aus der zweiten Mikrokapsel beginnt, wenn die Freisetzung des bioaktiven Moleküls aus der ersten Mikrokapsel abnimmt.
2. Zusammensetzung nach Anspruch 1, wobei die Copolymerarzneimittelträger Poly(D,L-Lactid-Co-Glycolid) sind.
3. Zusammensetzung nach Anspruch 2, wobei die Copolymerarzneimittelträger Molarverhältnisse von Lactid zu Glycolid von 40:60 bis 100:0 aufweisen.
4. Zusammensetzung nach Anspruch 1, wobei das bioaktive Molekül ein Peptid ist.
5. Zusammensetzung nach Anspruch 4, wobei das Peptid hormonell wirksam ist.
6. Zusammensetzung nach Anspruch 4, wobei das Peptid ein Luteinisierendes Hormon freisetzendes Hormon oder ein Analogon davon ist.
7. Zusammensetzung nach Anspruch 6, wobei das Luteinisierendes Hormon freisetzende Hormon [D-Trp⁶, des-Gly¹⁰]-LHRH-Ethylamid ist.
8. Zusammensetzung nach Anspruch 1, wobei das bioaktive Molekül ein Protein ist.
9. Zusammensetzung nach Anspruch 1, wobei das Gemisch aus mikroverkapseltem Peptid aus geeigneten Mengen an mit 3 Gew.-% beschicktem [D-Trp⁶, des-Gly¹⁰]-LHRH-Ethylamid, das in einem Copolymerarzneimittelträger mit einem Molverhältnis von 52% Lactid zu 48% Glycolid verkapselt ist, und an mit 10 Gew.-% beschicktem [D-Trp⁶, des-Gly¹⁰]-LHRH-Ethylamid, das in einem Copolymerarzneimittelträger mit einem Molverhältnis von 68% Lactid zu 32% Glycolid verkapselt ist, zusammengesetzt ist.
10. Zusammensetzung nach Anspruch 9, die außerdem noch eine dem Gemisch zugesetzte, geeignete Menge an mit 8 Gew.-% beschicktem [D-Trp⁶, des-Gly¹⁰]-LHRH-Ethylamid, das in einem Copolymerarzneimittelträger mit einem Molverhältnis von 85% Lactid zu 15% Glycolid verkapselt ist, enthält.
11. Zusammensetzung nach Anspruch 10, wobei das Gemisch [D-Trp⁶, des-Gly¹⁰]-LHRH-Ethylamid bei einer konstanten Geschwindigkeit von 50 µg bis 250 µg pro Tag während 180 Tagen freisetzt.
12. Zusammensetzung nach Anspruch 4, wobei das Peptid [D-N-Ac-4-CI-Phe², D-Trp⁶, D-Ala¹⁰]-LHRH oder ein LHRH-Antagonist-Analogon ist.
13. Zusammensetzung nach Anspruch 12, wobei das Gemisch [D-N-Ac-4-CI-Phe², D-Trp⁶, D-Ala¹⁰]-LHRH oder ein LHRH-Antagonist-Analogon bei einer konstanten Geschwindigkeit von ca. 200 µg pro Tag während mindestens 90 Tagen freisetzt.
14. Verfahren zur Herstellung einer Zusammensetzung für die parenterale Verabreichung nach Anspruch 1 zur Freisetzung einer wirksamen Menge einer konstanten Dosis eines bioaktiven Moleküls an ein Tier über eine vorgängig ausgewählte längere Zeitdauer, das folgende Stufen umfaßt:
 - a) Verkapselung von wirksamen Mengen des bioaktiven Moleküls in einem ersten und getrennt davon in einem zweiten biologisch abbaubaren und biologisch verträglichen Copolymerarzneimittelträger zur Bildung von ersten und zweiten Mikrokapseln, wobei jede Mikrokapsel zu einer anderen Geschwindigkeit für die Freisetzung des Moleküls befähigt ist, und
 - b) Mischung einer wirksamen Menge an ersten und zweiten Mikrokapseln zur Bildung der Zusammensetzung

mit einem Freisetzungsprofil, wobei die Diffusion des Moleküls durch die zweite Mikrokapsel beginnt, wenn die Freisetzung des bioaktiven Moleküls durch die erste Mikrokapsel abnimmt.

15. Verfahren nach Anspruch 14, wobei der erste und zweite Copolymerarzneimittelträger unterschiedliche Monomer-
verhältnisse besitzen.

16. Verfahren nach Anspruch 14, wobei der Arzneimittelträger aus der Gruppe, bestehend aus Polyacetalpolymeren, Polyorthoestern, Polyesteramiden, Polycaprolacton und Copolymeren davon, Polycarbonaten, Polyhydroxybutyrat und Copolymeren davon, Polymaleinamiden, Copolyoxalaten und Polysacchariden, ausgewählt wird.

Revendications

1. Composition pour administration parentérale pouvant délivrer une quantité effective d'une dose constante de molécule bioactive à un taux constant chez un animal pendant une période de temps longue et prédéterminée, comprenant un mélange de microcapsules libres dans lesquelles les quantités effectives de molécule bioactive sont encapsulées dans au moins deux excipients de copolymères biodégradables et biocompatibles pour former des premières et des secondes microcapsules, chaque excipient étant capable de libérer ladite molécule à des taux différents, ladite composition ayant un profil de libération dans lequel la libération de ladite molécule à travers ladite seconde microcapsule commence dès que la libération de ladite molécule bioactive à travers ladite première microcapsule décroît.

2. Composition selon la revendication 1, dans laquelle lesdits excipients copolymères sont des poly-(D,L-lactide-glycolide).

3. Composition selon la revendication 2, dans laquelle lesdits excipients copolymères ont un ratio molaire lactide, glycolide de 40 : 60 à 100 : 0 respectivement.

4. Composition selon la revendication 1, dans laquelle la molécule bioactive est une peptide.

5. Composition selon la revendication 4, dans laquelle ladite peptide est hormonalement active.

6. Composition selon la revendication 4, dans laquelle ladite peptide est une hormone lutérisante libérant une hormone ou analogue.

7. Composition selon la revendication 6, dans laquelle ladite hormone lutérisante libérant l'hormone est [D-Trp⁶, des-Gly¹⁰]-LHRH éthylamide.

8. Composition selon la revendication 1, dans laquelle la molécule bioactive est une protéine.

9. Composition selon la revendication 1, dans laquelle ledit mélange de peptide encapsulé est composé de quantités appropriées de 3% en poids de [D-Trp⁶, des-Gly¹⁰]-LHRH éthylamide, encapsulée dans une capsule de copolymère ayant un ratio molaire de 52% de lactide et de 48% de glycolide et chargé de 10% en poids de [D-Trp⁶, des-Gly¹⁰]-LHRH éthylamide encapsulé dans un excipient copolymère ayant un ratio molaire de 68% de lactide à 32% de glycolide.

10. Composition selon la revendication 9 et comprenant de plus une charge de 8% en poids de [D-Trp⁶, des-Gly¹⁰]-LHRH éthylamide encapsulé dans un excipient copolymère ayant un ratio molaire de 85% de lactide à 15% de glycolide ajouté audit mélange.

11. Composition selon la revendication 10, dans laquelle ledit mélange libère [D-Trp⁶, des-Gly¹⁰]-LHRH éthylamide à un taux constant de 50 µg à 250 µg par jour pendant 180 jours.

12. Composition selon la revendication 4, dans laquelle ladite peptide est [D-N-Ac-4,Cl-Phe²,D-Trp⁶,D-Ala¹⁰]-LHRH ou un LHRH antagoniste analogue.

13. Composition selon la revendication 12, dans laquelle ledit mélange libère [D-N-Ac-4,Cl-Phe²,D-Trp⁶,D-Ala¹⁰]-LHRH ou un LHRH antagoniste analogue à taux constant d'environ 200 µg par jour pendant au moins 90 jours.

14. Méthode de préparation d'une composition pour administration parentérale selon la revendication 1 pour libérer

une quantité effective d'une dose constante d'une molécule bioactive chez un animal sur une période de temps longue prédéterminée comprenant les étapes suivantes :

- 5 a) encapsulage des quantités effectives de ladite molécule bioactive dans un premier et second excipients copolymères biodégradables et biocompatibles, chacune desdites microcapsules libérant ladite molécule à un taux différent et,
- 10 b) combinaison d'une quantité effective des première et seconde microcapsules pour former ladite composition avec un profil de libération dans lequel la diffusion de ladite molécule à travers ladite seconde microcapsule commence lorsque la libération de ladite molécule bioactive à travers ladite première microcapsule décroît.

15 15. Méthode selon la revendication 14, dans laquelle lesdits premier et second excipients copolymères ont des ratios de monomères différents.

- 20 16. Méthode selon la revendication 14, dans laquelle ledit excipient est choisi dans le groupe comprenant les polymères polyacétol, polyorthoesters, polyesteramides, polycaprolactone et leurs copolymères, les polycarbonates, polyhydroxybutyrates et leurs copolymères, les polymaleamides, copolyoxalates et les polysaccharides.
- 25
- 30
- 35
- 40
- 45
- 50
- 55

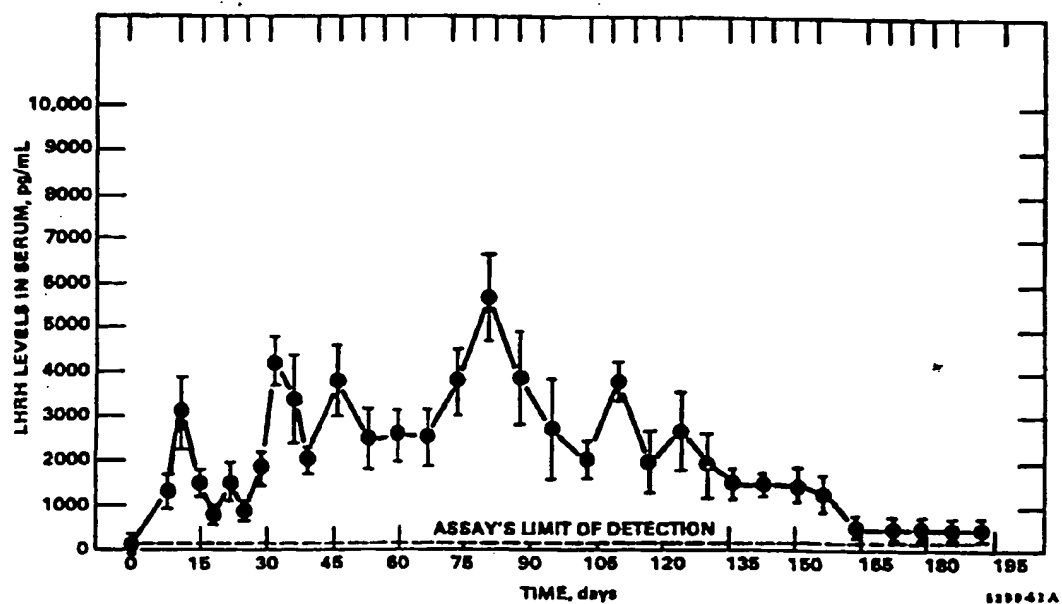


Figure 1.